Evaluation of the analgesic effect of ketamine as an additive to intrathecal bupivacaine in patients undergoing cesarean section

ARTICLE *in* ACTA ANAESTHESIOLOGICA TAIWANICA · FEBRUARY 2014

DOI: 10.1016/j.aat.2013.12.004

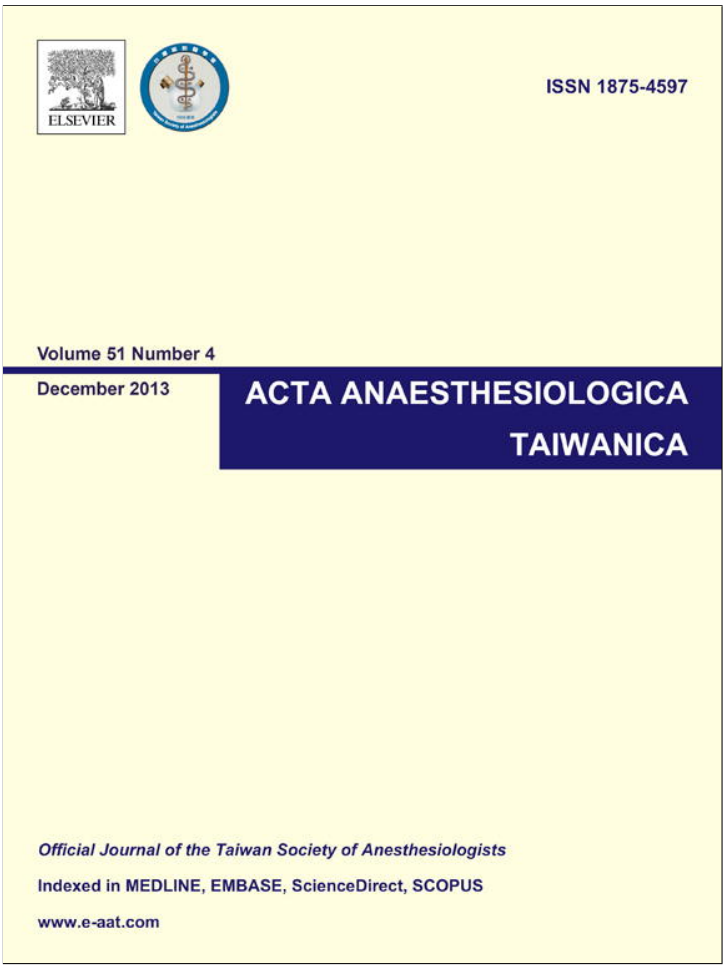
3 AUTHORS, INCLUDING:

Marzeih Khezri
Qazvin University of Medical Sciences
30 PUBLICATIONS **27** CITATIONS

SEE PROFILE

Navid Mohammadi
Iran University of Medical Sciences
35 PUBLICATIONS **36** CITATIONS

SEE PROFILE



Acta Anaesthesiologica Taiwanica 51 (2013) 155–160

Contents lists available at ScienceDirect

Acta Anaesthesiologica Taiwanica

journal homepage: www.e-aat.com

Original Article

Evaluation of the analgesic effect of ketamine as an additive to intrathecal bupivacaine in patients undergoing cesarean section

Marzieh Beigom Khezri [1]*, Javad Ghasemi [2], Navid Mohammadi [3]

[1] Department of Anesthesiology, Faculty of Medicine, Qazvin University of Medical Science, Qazvin, Iran
[2] Department of Anesthesiology, Qazvin University of Medical Science, Qazvin, Iran
[3] Department of Community and Preventive Medicine, Faculty of Medicine, Iran University of Medical Sciences, Iran

ARTICLE INFO

Article history:
Received 11 April 2013
Received in revised form
30 September 2013
Accepted 3 October 2013

Key words:
cesarean section;
injections;
spinal;
intrathecal;
pain

ABSTRACT

Objective: Nowadays, conventional analgesic agents, which are widely used for pain relief after cesarean section, provide suboptimal analgesia with occasional serious side effects. We designed a randomized, double-blind, placebo-controlled study to evaluate the analgesic efficacy of intrathecal ketamine added to bupivacaine after cesarean section.

Methods: Sixty patients scheduled for cesarean section under spinal anesthesia were randomly allocated to one of the two groups to receive either bupivacaine 10 mg combined with 0.1 mg/kg ketamine, or bupivacaine 10 mg combined with 0.5 mL distilled water intrathecally. The time to the first analgesic request, analgesic requirement in the first 24 hours after surgery, onset times of sensory and motor blockades, the durations of sensory and motor blockades, and the incidences of adverse effects such as hypotension, ephedrine requirement, bradycardia, and hypoxemia, were recorded.

Results: Patients who received ketamine had a significantly prolonged duration of anesthesia compared with those who did not in the control group [95% confidence intervals (CI) 195–217; $p = 0.001$]. The mean time to the first analgesic request was also significantly longer in ketamine group (95% CI 252.5–275; $p < 0.001$). The total analgesic consumption in the 24 hours following surgery significantly lessened in the ketamine group compared with that of the control group (95% CI 2–2.5; $p < 0.001$). The two groups did not differ significantly in intraoperative and postoperative side effects.

Conclusion: Intrathecal ketamine 0.1 mg/kg co-administered with spinal bupivacaine elongated the time to the first analgesic request and lessened the total analgesic consumption in the first 24 postoperative hours in comparison with bupivacaine alone in the control group following elective cesarean delivery.

1. Introduction

Pain control after cesarean delivery is associated with improved breastfeeding and infant rooming in. However, in parturient women, we must balance the benefits of analgesia and known fetal and maternal side effects induced, including bradycardia, respiratory depression, arterial hypotension, emetogenesis, and pruritus.[1]

Currently, opioids are widely used for pain relief, but they often provide sub-optimal analgesia with occasional serious side effects. Furthermore, it is reported that only a single administration of an opioid may also induce a long lasting reduction of threshold of pain sensitivity, leading to delayed hyperalgesia.[2] Therefore, the search for a new drug that may decrease the severity of postoperative pain with minimal side effects seems mandatory. It is well known that the activation of spinal N-methyl-D-aspartate (NMDA) receptors is involved in the development of hyperalgesia.[3] Adjusting regional anesthesia with NMDA antagonists such as ketamine and magnesium so as to reduce the postoperative pain in patients undergoing abdominal or orthopedic surgery is practicable.[4,5] In a systemic review of 24 studies, it was reported that ketamine has a significant immediate and preventive analgesic benefit in 58% of the studies (including both intravenous and neuraxial administration).[6] Similar efficacy of reduced opioid consumption was concluded from a systemic review of 37 randomized trials of ketamine when given in small doses in the preoperative period.[7] In previous studies, it was shown that the addition of ketamine to bupivacaine in spinal anesthesia results in stable haemodynamics.[8,9]

Conflicts of interest: All authors declare no conflicts of interest.

* Corresponding author. Department of Anesthesiology, Faculty of Medicine, Qazvin University of Medical Science, Shahid Bahonar Boulevard, P.O. Box 3419759811, Qazvin, Iran.
E-mail: mkhezri@qums.ac.ir, mkhezri88@gmail.com (M.B. Khezri).

1875-4597/$ – see front matter
http://dx.doi.org/10.1016/j.aat.2013.12.004

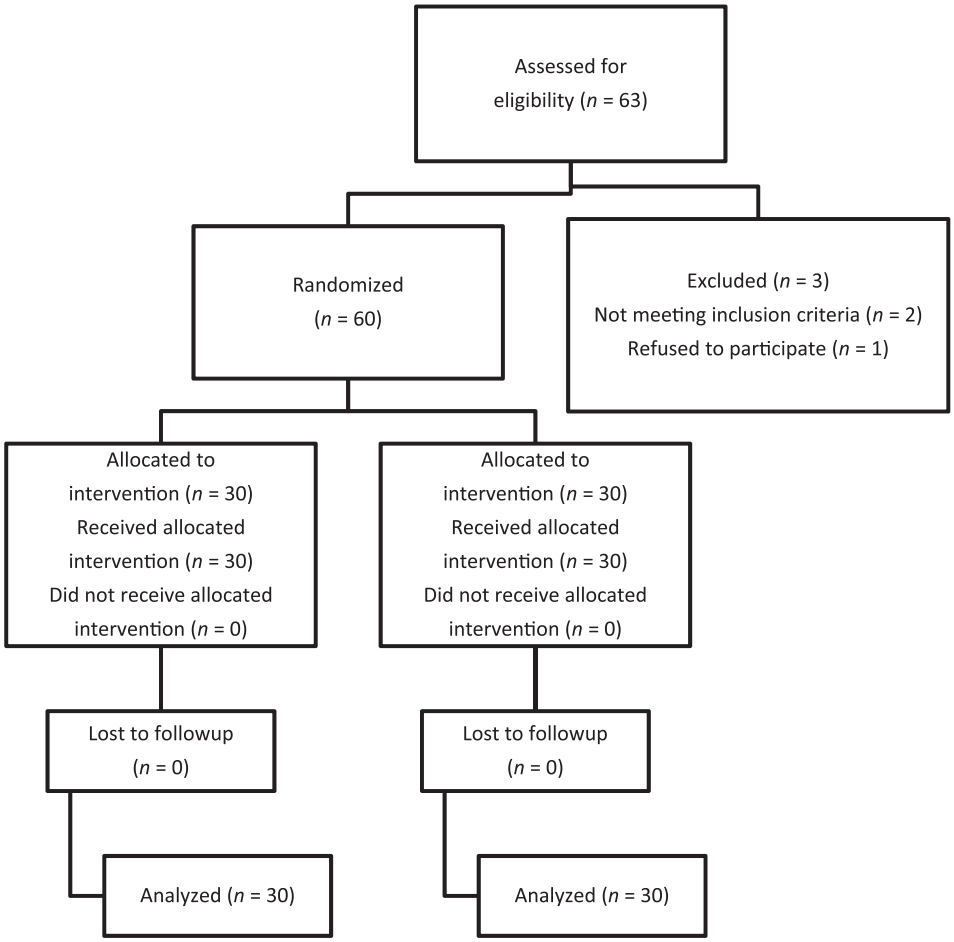


Fig. 1. Consort flow diagram of the trial.

However, despite extensive discourses, there is still controversy in the literature as to the safety and analgesic efficacy of ketamine through the intrathecal route.[10–15] Preservative-free racemic ketamine was shown to be devoid of neurotoxic effects after both single and repeated administration in animals.[10–12] Borgbjerg and Svenssson[12] administered preservative-free ketamine 5 mg intrathecally to rabbits for 14 consecutive days and concluded that it bore no evidence of harmful neurotoxic effects, even after repeated injections. It is suggested that various factors, like preservatives (chlorobutanol and benzethonium chloride),the use of multiple drugs for an extended period of time, and the indwelling intrathecal catheters may be responsible for neurological complications.[10–14] By contrast, Yu et al[15] reported that ketamine provided potent protective effects against the ischemic reperfusion induced spinal cord injuries. Furthermore, in obstetrics, ketamine has no detrimental effect on uterine blood flow, and maternal or fetal hemodynamics.[16] Moreover, Horacek et al[17] declared that a subanesthetic dose of ketamine infusion induced changes similar to those by monoamineric-based antidepressants, and that the reduction in theta cordance could be a marker and a predictor of the fast-acting antidepressant effect of ketamine. Therefore, these beneficial effects may be valuable when ketamine is used as an adjunct for spinal anesthesia in obstetric settings.

We hypothesized that ketamine might provide better pain relief after cesarean section than conventional anesthetic agents. In addition, unlike spinal opioids, ketamine does not produce pruritus, respiratory depression, hemodynamic instability, or hyperalgesia. In order to test our hypothesis, we designed this randomized, double-blind, placebo-controlled study to evaluate the postoperative analgesic effects of intrathecal ketamine added to spinal bupivacaine in patients undergoing cesarean section.

2. Methods

The present study was a placebo-controlled, randomized, double-blind clinical trial in which the patients, investigators, and anesthesiologists were blinded to the designed treatment. Patients were fully informed about the study protocol and submitted written informed consent. The study was approved by the institutional ethics committee and performed during July 2011 to February 2012. Exclusion criteria included significant coexisting complications such as hepatorenal and cardiovascular diseases, any contraindication to regional anesthesia such as local infection or bleeding disorders, allergy to ketamine, long-term opioid use, or a history of chronic pain. Using a computer-generated randomization schedule, 60 patients aged 18–45, American Society of Anesthesiologists (ASA) physical status I or II, scheduled for cesarean section under spinal anesthesia, were randomly allocated to one of the two groups of 30 participants each. The Consolidated Standards of Reporting Trials (CONSORT) recommendations for reporting randomized, controlled clinical trials[18] were followed (Fig. 1). Blinding was achieved through the use of equal amounts of the study drugs (2.5 mL) and the contain syringes used were labeled A and B according to their content. Identically coded syringes prepared by the operating room personnel who were not involved in the study, were randomly handed to the anesthetist, who was unaware of the

identities of the drugs. The ketamine group (Group K) received intrathecal bupivacaine 10 mg combined with 0.1 mg/kg ketamine (Trittau, Germany), and the control group (Group C) received intrathecal bupivacaine (Mylan S.A.S. Saint-Priest, France) 10 mg combined with 0.5 mL distilled water. All patients were given an intravenous preload of lactated Ringer's solution at 5–7 mL/kg prior to the subarachnoid block. With an aseptic technique, a 25-gauge Quincke needle was inserted intrathecally via a midline approach at the L4-5 interspace by the anesthetist, who was unaware of patient assignment, while the patient was in the sitting position. Following a successful dural puncture, the anesthetic solution was injected. The primary outcomes of this randomized, double-blind, placebo-controlled clinical trial were to evaluate the time to the first requirement of analgesic supplement and the total analgesic consumption in the first 24 postoperative hours. In this study, postoperative analgesia was defined as the time from the intrathecal injection of anesthetic solution to the first requirement of analgesic supplement. No additional analgesic was administered unless requested by the patient. Patients were elucidated preoperatively for the use of the verbal rating scale (VRS) from zero to 10 (0 = no pain, 10 = maximum imaginable pain) for pain assessment. If the VRS exceeded four and the patient requested a supplement analgesic, diclofenac Na Suppository 100 mg was given as postoperative pain relief. If the time of administration from diclofenac Na to patients' request was less than 8 hours, intravenous pethidine 25 mg was given for breakthrough pain relief (VRS > 4). The secondary outcome of this study included the assessment of sensory block onset time, maximum sensory level, onset of motor block, duration of blockade, hemodynamic variables, the incidence of hypotension, ephedrine requirements, bradycardia, hypoxemia (saturation of peripheral oxygen < 90), pruritus, nausea, and vomiting. Sensory block was assessed with a pinprick test. The onset of sensory block was defined as the time from the end of injection of the intrathecal anesthetic to the time at which pain at the T10 dermatome was absent; the duration of sensory block was defined as the time from the maximum block height to the T10 dermatome to regression of block, as evaluated by the pinprick test. The maximal level of sensory block was evaluated by the pinprick test after 20 minutes following the completion of injection. The duration of spinal anesthesia was defined as the time from injection of spinal anesthetic to the first occasion when the patient complained of pain in the postoperative period. Motor block was assessed by the modified Bromage score (0 = no motor loss; 1 = inability to flex the hip; 2 = inability to flex the knee; and 3 = inability to flex the ankle); the onset of motor block was defined as the time from intrathecal injection to Bromage block one, whereas the duration of motor block was assumed when the modified Bromage score was zero.

Mean arterial pressure (MAP) and heart rate (HR) were recorded by an observer blinded to the patient group assignment, 5 minutes prior to the intrathecal injection and 2 minutes, 4 minutes, 6 minutes, 8 minutes, 10 minutes, 15 minutes, and 20 minutes after the injection. If the systolic blood pressure (SBP) fell to 20% below the baseline (in the ward) or was < 90 mmHg, ephedrine 5 mg was administered intravenously. Also, if HR was < 50 beats/minute, atropine sulfate 0.5 mg was administered intravenously. A follow-up telephone call was made 24 hours following the surgery and again 1 month and 6 months later, during which the patients were asked about the side effects, and dysesthesia of the lower limbs or buttocks. The study data were collected and analyzed by a member of the statistics department who was not involved in the study. To calculate the sample size, data of previous similar studies were taken into consideration.[19–21] Sample size analysis determined that a total of 25 patients ($n = 25$) per group was required to detect a 20 minute difference in the median duration of analgesia between the groups using the Mann–Whitney U test, with a power of 0.9 and an α equal to 0.05. We assigned 30 patients to each group to allow for dropouts and protocol violations. Data were analyzed using SPSS (version 15.0, SPSS Inc., Chicago, IL, USA). Parametric data were expressed as mean and standard deviation (SD) and analyzed using the independent t test. Continuous variables were tested for normal distribution by the Kolmogorov-Smirnov test. Values normally distributed were expressed as mean (SD) and those not normally distributed were expressed as median (range). Nonparametric data were expressed as median and interquartile range and analyzed using the Mann–Whitney U test. The effect of time on hemodynamic parameters was analyzed using the repeated measurement analysis of variance. The χ^2 test was used to analyze the incidence of adverse events. Pain scores, motor scores, and sensory level were evaluated within the study groups using the Wilcoxon's signed rank test. A p value < 0.05 was considered statistically significant.

3. Results

Among 63 patients initially enrolled in this study, three patients were excluded because of logistic reason or violation of the study protocol. Sixty patients were included and randomly assigned to two groups for the study (Fig. 1).

There were no significant differences in age, height, and weight between the two groups. The duration of surgery was also similar in the two groups (Table 1).

The mean onset time of sensory block was 91.00 ± 20.98 seconds in Group K and 78.5 ± 26.0 seconds in Group C. The difference between Groups K and C (95% CI = 77.5–90; $p = 0.045$) was significant. The mean duration of sensory block time was 143.73 ± 17.7 minutes in Group K and 133.53 ± 32.68 minutes in Group C. The difference between two groups ($p = 0.139$) was shown to be insignificant. The mean onset time of motor block was 88.66 ± 31.67 seconds in Group K and 81.8 ± 27.2 seconds in Group C, with no statistically significant difference between the two groups ($p = 0.374$). The mean duration of motor blockade time in Group K (170.43 ± 22.70 minutes) was longer than that in Group C (143.16 ± 33.94 minutes), showing a statistically significant difference between the two groups (95% CI = 147.5–165; $p = 0.001$). As shown in Table 2, the patients receiving ketamine had a significantly prolonged duration of anesthesia compared with those in the control group (95% CI = 195–217; $p = 0.001$). Similarly, the mean time to the first analgesic request was also significantly longer in Group K (297.80 ± 31.48 minutes) than in Group C (236.34 ± 22.20 minutes) and the difference was significant (95% CI = 252.5–275; $p < 0.001$). Likewise, the total analgesic consumption in the 24 hours following surgery was significantly less in Group K as compared with the control group (95% CI = 2–2.5; $p < 0.001$).

Despite aqueous volume loading prior to anesthetic block, transient hypotension occurred at various time points in the two groups. These patients were treated with 5 mg boluses of intravenous ephedrine to maintain the fall of SBP within 20% of the baseline value or at 90 mmHg. The mean variation of MAP and

Table 1
Demographic data for the two study groups.

	Group K ($n = 30$)	Group C ($n = 30$)	p
Age (y)	27.22 ± 5.81	26.55 ± 6.05	0.505
Weight (kg)	88.5 ± 13.6	89.7 ± 11.9	0.934
Height (cm)	161 ± 8.4	161 ± 6.1	0.743
Duration of surgery (min)	81.4 ± 17.6	81.7 ± 18.8	0.840

Values are presented as mean ± standard deviation.
C = control; K = ketamine.

Table 2
Characteristics of spinal anesthesia.

	Group K ($n = 30$)	Group C ($n = 30$)	p
Onset time of sensory block (s)	91.00 ± 20.98	78.5 ± 26.0	0.045
Duration of sensory block (min)	143.73 ± 17.7	133.53 ± 32.68	0.139
Onset time of motor block (s)	88.66 ± 31.67	81.8 ± 27.2	0.374
Duration of motor block (min)	170.43 ± 22.70	143.16 ± 33.94	<0.001
Time to first request of analgesia (min)	297.80 ± 31.48	236.34 ± 22.20	<0.001
Duration of spinal anesthesia (min)	223.83 ± 41.59	192.33 ± 30.36	0.003
Total ephedrine requirement (mg)	1.83 ± 3.82	3.82 ± 5.20	0.088
Total analgesic consumption in 24 h (number of analgesia requests)	2(1–3)	3(2–3)	<0.001

Data are presented as mean ± standard deviation except for total analgesic consumption in 24 hours, which is presented as median ± interquartile range.
C = control; K = ketamine.

HR was defined as the difference between the highest and the lowest MAP and HR. The mean variation of MAP was 50.00 ± 76.14 in Group C and 25.78 ± 11.64 in Group K. The difference between the two groups was insignificant ($p = 0.090$). The mean variation of HR was 32.86 ± 10.17 in Group C and 33.90 ± 11.62 in Group K, the difference of which was not statistically significant ($p = 0.715$). Table 3 shows the repeated measures analysis carried out to see the trend of change in HR and MAP in the intraoperative period.

Although the mean of total ephedrine requirement in Group K (1.83 ± 3.82 mg) was less than that of Group C (3.83 ± 5.20 mg), the overall difference in ephedrine requirement between the two groups was statistically insignificant ($p < 0.088$). As shown in Table 4, the two groups did not differ significantly in intraoperative and postoperative side effects including pruritus, nausea, vomiting, headache, shivering, and respiratory depression.

No patient in either group had any sensory or motor complications identified within the 6 months following surgery. All newborns in our study were free of any adverse effects.

4. Discussion

Based on the data found in the present study, it could be concluded that in Group K the administration of intrathecal ketamine 0.1 mg/kg with spinal bupivacaine could cause a prolonged intraoperative anesthesia and increase the time for the first request for anesthetic after cesarean delivery, as compared with the control group. Although these findings are consistent with those of some previous studies,[5,22–24] there are still conflicting data regarding the effect of ketamine on postoperative analgesic consumption in other studies.[19,21] However, analgesic properties of ketamine are shown to depend on antagonizing spinal NMDA receptors . It is well known that the activation of spinal NMDA receptors induces hyperalgesia. Moreover, it is reported that NMDA receptor antagonists have a preventive effect on preoperative pain and may enhance the efficacy of treatment of both acute and prolonged postsurgical pain.[5] Furthermore, ketamine blocks the voltage-sensitive calcium channels, depresses sodium channels, and alters cholinergic neurotransmission, which is implicated in pain mechanisms; it also acts as a noradrenergic and serotonergic uptake inhibitor, which is involved in descending antinociceptive pathways.[25] In a recent study by Yang et al,[26] it is reported that intrathecal ketamine

Table 3
Changes in hemodynamic variables.

	HR		MAP	
	Group K n = 30)	Group C (n = 30)	Group K (n = 30)	Group C (n = 30)
5 min prior to SA	100.90 ± 13.16	98.73 ± 13.61	94.93 ± 3.41	95.05 ± 5.36
2 min after SA	97.06 ± 15.15	101.73 ± 16.15	79.34 ± 15.97	74.76 ± 15.95
4 min after SA	92.23 ± 12.36	97.26 ± 15.03	80.97 ± 3.07	74.93 ± 13.71
6 min after SA	92.26 ± 12.44	98.90 ± 17.58	85.74 ± 9.60	82.12 ± 12.61
8 min after SA	87.56 ± 14.40	92.73 ± 17.36	91.41 ± 6.83	87.54 ± 10.57
10 min after SA	88.36 ± 17.71	91.70 ± 13.68	91.27 ± 5.15	89.11 ± 7.93
15 min after SA	92.40 ± 16.87	89.13 ± 14.32	90.83 ± 5.77	92.66 ± 9.09
20 min after SA	94.13 ± 18.49	88.26 ± 14.49	89.73 ± 5.56	82.96 ± 5.27
25 min after SA	93.83 ± 15.75	90.86 ± 12.33	86.14 ± 4.52	86.38 ± 4.66
30 min after SA	93.16 ± 14.83	89.50 ± 11.36	107.70 ± 76.69	86.97 ± 6.53
p	0.803		0.59	

Data are presented as mean ± standard deviation.
C = control; HR = heart rate (bpm); K = ketamine; MAP = mean arterial blood pressure (mmHg); SA = spinal anesthesia.

produces noticeable antinociception effects in rats and inhibits the enhanced protein kinase C expression in the spinal dorsal horn in response to formalin-induced pain.

The second observation which should be considered is that the overall analgesic consumption in the first 24 hours in Group K was less than that found in the control group. This finding is also consistent with most previous studies.[27–30] Results of the study by Laulin et al[27] indicated that sustained NMDA receptor blocking by ketamine may improve postoperative morphine effectiveness. In a systematic analysis of qualified clinical trials, Walker et al[28] also suggested that intrathecal racemic ketamine and Esketamine could potentiate the antinociceptive effects of intrathecal morphine.[29] Co-infused intrathecal ketamine attenuated morphine tolerance to both somatic and visceral antinociception in animal models.[30] The authors of the present study speculate that ketamine significantly enhances the pethidine effects on postoperative pain management, thereby preventing the subsequent NMDA activation. The NMDA receptor antagonist potentiates the opioid antinociception by blocking the spinal C-fiber stimulation.[27] Analgesic consumption is known to be interrelated with primary hyperalgesia caused by the augmentation of the sensitivity of primary afferent receptors, rather than by central sensitization.[27] Although the results of our study are consistent with those of most previous studies,[27–29,31] on

Table 4
Side effects.

	Group K ($n = 30$)	Group C ($n = 30$)
Pruritus	1 (3.33)	0
Respiratory depression	0	0
Hypotension	7 (23.3)	8 (26.7)
Bradycardia	0	0
Nausea	1 (3.33)	3 (10)
Vomiting	0	1 (3.33)
Headache	0	0
Shivering	2 (6.7)	4 (13.3)

Data are presented as number of patients (%).
C = control; K = ketamine.

the contrary, Kathirvel et al[21] showed that 25 mg of intrathecal esketamine (IT S ketamine) + ketamine spared the local anesthetic effect of bupivacaine, but failed to provide extended postoperative analgesia or decrease the postoperative analgesic requirements. The discrepancy of the results may be due to different methodologies and populations. For example, Kathirvel et al[21] used a higher dose (10 mg) of bupivacaine in the control group than that in the ketamine group (7.5 mg). In this study, we used 10 mg bupivacaine in both groups.

The third observation which should be noted is that the administration of 0.1 mg/kg intrathecal ketamine with spinal bupivacaine prolonged the onset of sensory block, whereas on the contrary, the results by Unlugenc et al[19] and Yanli and Eren[31] suggested that the addition of intrathecal ketamine to spinal bupivacaine shortened the onset of both sensory and motor blockades. By contrast, Murali Krishna et al[20] reported that the onset of sensory or motor block was also similar in the two groups. However, these apparently controversial results may be due to the different populations, doses of ketamine, and methodologies. In our study, we used distilled water in the control group and ketamine 0.1 mg/kg in the ketamine group combined with spinal bupivacaine. The authors of the present study speculate that the pH of the solution is a possible reason why ketamine prolongs the onset of sensory block. The pH of ketamine hydrochloride is slightly acidic (3.5–5.5), whereas the pH of distilled water (which we used in the control group) is neutral (pH 7–7.4). Results of the clinical study by Galindo[32] suggested that the pH-adjusted solutions of local anesthetics produced a more rapid onset of blockade with better quality and longer duration than the unmodified commercial preparations. Moreover, Ritchie et al[33] confirmed that the uncharged molecule is essential for penetration to the intracellular receptor site. The addition of ketamine decreases the pH of bupivacaine and therefore, the onset of the sensory block is prolonged.

The next observation which should be taken into account is that the addition of intrathecal ketamine 0.1 mg/kg to spinal bupivacaine prolonged the duration of motor block with the sensory block remaining untouched. This finding is in agreement with that found in the study by Govindan et al,[34] in which they claimed that the motor blockade by intrathecal ketamine was longer than the sensory blockade. By contrast, Togal et al[9] described that the intrathecal Esketamine administered with a low dose of spinal bupivacaine provided a shorter duration of action and less motor blockade in elderly males. The results obtained by Togal et al[9] may be due to the utilization of a lower dose of bupivacaine in the ketamine group. However, the discrepancy in the results of different studies is probably due to the application of different methodologies and populations.

In our study, the mean of total ephedrine requirement in Group K was less than that in Group C; nevertheless, the overall difference in ephedrine requirement between the two groups was statistically insignificant, yet the difference was obvious in the clinical settings. The overall results of our study are consistent with studies by Bion,[8] Murali Krishna et al[20], and Kathirvel et al,[21] who declared that the use of intrathecal ketamine was associated with minimal hemodynamic fluctuations. Bion[8] reported that the transmission of ketamine into the venous system (azygos vein) of the spinal cord induced cardiovascular stimulation and hemodynamic stability after spinal anaesthesia.[8]

The selection of a dose of intrathecal ketamine of 0.1 mg/kg was based on the fact that several previous studies showed that the use of such a dose could prolong the duration of analgesia without additional side effects.[9,20] By contrast, the endogenous opioid analgesic system is enhanced by pregnancy during labor and the early postpartum period, leading to reduced analgesic requirement.[35] In our study, because the patients were pregnant, we used a low dose of ketamine (0.1 mg/kg) in combination with spinal bupivacaine 10 mg.

In the present study, we did not find any incidence of behavioral, psychomimetic, or neurological complications in the patients receiving ketamine intrathecally. This result is in harmony with the findings by Bion,[8] who reported that intrathecal ketamine acts locally on the spinal cord nociceptors and does not act systemically after being absorbed into the bloodstream. The second possible cause of this finding is that we used a lower dose (0.1 mg/kg) of ketamine compared with those of previous studies.[36] Hawksworth and Serpell[36] observed psychomimetic manifestations in 50% and 30% of their patients while using intrathecal ketamine at doses of 0.75–0.9 mg/kg, respectively. Conversely, Togal et al[9] used a low dose ketamine (0.1 mg/kg) and observed no side effects.[9] However, it seems that the incidence of complications with intrathecal ketamine is a dose-dependent phenomenon and thus the routine use of such drugs in clinical practice should be postponed until its safety is proved by further studies.

In conclusion, based on the data found in our study, it could be concluded that intrathecal ketamine 0.1 mg/kg with spinal bupivacaine caused a prolonged intraoperative anesthesia, increased the time to the first analgesic request, and decreased the total analgesic consumption in the first 24 postoperative hours as compared with the control group following elective cesarean delivery.

Acknowledgments

Registration number: ACTRN12611000729921 and Clinical trials.gov Identifier: NCT01404442. The authors thank Kosar Hospital Research Center.

References

1. Chaney MA. Side effects of intrathecal and epidural opioids. *Can J Anesth* 1995;**42**:891–903.
2. Laulin JP, Célèrier E, Larcher A, Le Moal M, Simonnet G. Opiate tolerance to daily heroin administration: apparent phenomenon associated with enhanced pain sensitivity. *Neuroscience* 1999;**89**:631–6.
3. Ren K, Williams GM, Hylden JLK, Ruda MA, Dubner R. The intrathecal administration of excitatory amino acid receptor antagonists selectively attenuated carrageenan-induced behavioral hyperalgesia in rats. *Eur J Pharmacol* 1992;**219**:235–43.
4. Khezri MB, Yaghobi S, Hajikhani M, Asefzadeh S. Comparison of postoperative analgesic effect of intrathecal magnesium and fentanyl added to bupivacaine in patients undergoing lower limb orthopedic surgery. *Acta Anaesthesiol Taiwan* 2012;**50**:19–24.
5. Lavand'homme P, De Kock M, Waterloos H. Intraoperative epidural analgesia combined with ketamine provides effective preventive analgesia in patients undergoing major digestive surgery. *Anesthesiology* 2005;**103**:813–20.
6. McCartney CJ, Sinha A, Katz J. A qualitative systemic review of the role of N-methyl-D-aspartate receptor antagonists in preventive analgesia. *Anesth Analg* 2004;**98**:1385–400.
7. Subramaniam K, Subramaniam B, Steinbrook RA. Ketamine as adjuvant analgesic to opioids: a quantitative and qualitative systemic review. *Anesth Analg* 2004;**99**:482–95.
8. Bion JF. Intrathecal ketamine for war surgery. A preliminary review. *Anaesthesia* 1984;**39**:1023–8.
9. Togal T, Demirbelik S, Koroglu A, Yapici E, Ersoy O. Effects of S (+) ketamine added to bupivacaine for spinal anesthesia for prostate surgery in elderly patients. *Eur J Anaesthesiol* 2004;**21**:193–7.
10. Malinovsky JM, Lepage JY. Is ketamine or its preservative responsible for neurotoxicity in the rabbit? *Anesthesiology* 1993;**78**:109–15.
11. Rojas AC, Alves JG, Moreira E Lima R, Esther Alencar Marques M, Moreira de Barros GA, Fukushima FB, et al. The effects of subarachnoid administration of preservative-free S(+)-ketamine on spinal cord and meninges in dogs. *Anesth Analg* 2012;**114**:450–5.
12. Borgbjerg FM, Svenssson BA. Histopathology after repeated intrathecal injections of preservative free ketamine in the rabbits: a light and electron microscopic examination. *Anesth Analg* 1994;**79**:105–11.
13. Vranken JH, Troost D, Wegener JT, Kruis MR, van der Vegt MH. Neuropathological finding after continuous intrathecal administration of S(+) ketamine for the management of neuropathic cancer pain. *Pain* 2005;**117**:231–5.

14. Vranken JH, Troost D, de Haan P, Pennings FA, van der Vegt MH, Dijkgraaf MG, et al. Severe toxic damage to the rabbit spinal cord after intrathecal administration of preservative-free S (1) ketamine. *Anesthesiology* 2006;**105**:813–8.
15. Yu QJ, Zhou QS, Huang HB, Wan YL, Tian SF, Duan DM. Effects of ketamine on the balance of ions Ca^{2+}, Mg^{2+}, Cu^{2+} and Zn^{2+} in the ischemia-reperfusion affected spinal cord tissues in rabbits. *Neurochem Res* 2009;**34**:2192–6.
16. Strumper D, Gogarten W, Durieux ME, Hartleb K, Van Aken H, Marcus MA. The effects of S+ketamine andracemic ketamine on uterine blood flow in chronically instrumented pregnant sheep. *Anesth Analg* 2004;**98**:497–502.
17. Horacek J, Brunovsky M, Novak T, Tislerova B, Palenicek T, Bubenikova-Valesova V, et al. Subanesthetic dose of ketamine decreases prefrontal theta cordance in healthy volunteers: implications for antidepressant effect. *Psychol Med* 2010;**40**:1443–51.
18. Moher D, Schulz KF, Altman DG. The CONSORT statement: revised recommendations for improving the quality of reports of parallel group randomized trial. *BMC Med Res Methodol* 2001;**1**:2.
19. Unlugenc H, Ozalevli M, Gunes Y, Olguner S, Evrüke C, Ozcengiz D, et al. A double-blind comparison of intrathecal S(+) ketamine and fentanyl combined with bupivacaine 0.5% for caesarean delivery. *Eur J Anaesthesiol* 2006;**23**:1018–24.
20. Murali Krishna T, Panda NB, Batra YK, Rajeev S. Combination of low doses of intrathecal ketamine and midazolam with bupivacaine improves postoperative analgesia in orthopaedic surgery. *Eur J Anaesthesiol* 2008;**25**:299–306.
21. Kathirvel S, Sadhasivam S, Saxena A, Kanan TR, Ganjoo P. Effects of intrathecal ketamine added to bupivacaine for spinal anaesthesia. *Anaesthesia* 2000;**55**:899–910.
22. Sator-Katzenschlager S, Deusch E, Maier P, Spacek A, Kress HG. The long-term antinociceptive effect of intrathecal S(+)-ketamine in a patient with established morphine tolerance. *Anesth Analg* 2001;**93**:1032–4.
23. Vranken JH, van der Vegt MH, Kal JE, Kruis MR. Treatment of neuropathic cancer pain with continuous intrathecal administration of S (+)-ketamine. *Acta Anaesthesiol Scand* 2004;**48**:249–52.
24. Hama A, Basler A, Sagen J. Enhancement of morphine antinociception with the peptide N-methyl-D-aspartate receptor antagonist [Ser1]-histogranin in the rat formalin test. *Brain Res* 2006;**1095**:59–64.
25. Quibell R, Prommer EE, Mihalyo M, Twycross R, Wilcock A. *Ketamine. J Pain Symptom Manage* 2011;**41**:640–9.
26. Yang Y, Guo QL, Zou WY, Wang E, Yan JQ. Effect of intrathecal ketamine injection on protein kinase C expression in the spinal dorsal horn of rats with formalin-induced pain. *Nan Fang Yi Ke Da Xue Xue Bao* 2011;**31**:461–4 [In Chinese].
27. Laulin JP, Maurette P, Corcuff JB, Rivat C, Chauvin M, Simonnet G. The role of ketamine in preventing fentanyl-induced hyperalgesia and subsequent acute morphine tolerance. *Anesth Analg* 2002;**94**:1263–9.
28. Walker SM, Goudas LC, Cousins MJ, Carr DB. Combination spinal analgesic chemotherapy: a systematic review. *Anesth Analg* 2002;**95**:674–715.
29. Joó G, Horvath G, Klimscha W, Kekesi G, Dobos I, Szikszay M, et al. The effects of ketamine and its enantiomers on the morphine- or dexmedetomidine induced antinociception after intrathecal administration in rats. *Anesthesiology* 2000;**93**:231–41.
30. Miyamoto H, Saito Y, Kirihara Y, Hara K, Sakura S, Kosaka Y. Spinal coadministration of ketamine reduces the development of tolerance to visceral as well as somatic antinociception during spinal morphine infusion. *Anesth Analg* 2000;**90**:136–41.
31. Yanli Y, Eren A. The effect of extradural ketamine on onsettime and sensory block in extradural anaesthesia with bupivacaine. *Anaesthesia* 1996;**51**:84–6.
32. Galindo A. pH-Adjusted local anesthetics: clinical experience. *Reg Anaesth* 1983;**8**:35–6.
33. Ritchie JM, Ritchie B, Greengard P. The active structure of local anesthetics. *J Pharmacol Exp Ther* 1965;**150**:152–9.
34. Govindan K, Krishnan R, Kaufman MP, Michael R, Fogler RJ, Gintautas J. Intrathecal ketamine in surgeries for lower abdomen and lower extremities. *Proc West Pharmacol Soc* 2001;**44**:197–9.
35. Bacigalupo G, Riese S, Rosendahl H, Saling E. Quantitative relationships between pain intensities during labor and beta-endorphin and cortisol concentrations in plasma: decline of the hormone concentrations in the early postpartum period. *J Perinat Med* 1990;**18**:289–96.
36. Hawksworth C, Serpell M. Intrathecal anaesthesia with ketamine. *Reg Anesth Pain Med* 1998;**23**:283–8.